Volume 4

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

Before The Honorable Richard Seeborg, Judge

IN RE: VIAGRA (SILDENAFIL CITRATE) AND CIALIS (TADALAFIL) PRODUCTS LIABILITY LITIGATION.	**NO. 16-md-02619 RS**
This Document Relates to: All Actions	

San Francisco, California
Tuesday, October 22, 2019

TRANSCRIPT OF PROCEEDINGS

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I N D E X

Tuesday, October 22, 2019 - Volume 4

Tuesday - October 22, 2019 **9:00 a.m.**

P R O C E E D I N G S

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THE CLERK: Calling case 3-16-md-2691, In Re Viagra Products Liability Litigation.

THE COURT: I'm going to dispense with having the appearances. I know you-all now. I think we can just get right into it.

Welcome back, by the way.

So today is our day for closing arguments putting in context what we heard last week. I'm looking forward to that because I have such very fine lawyers here so I'm sure they will give me a lot of help, which I need.

So, you know, the motions are -- I think the defense brought the motions if we were looking at it purely from the initial moving party's standpoint, but I still think it would be helpful, I would prefer to hear from plaintiffs first and then from the defendants because it really was presented in almost a minitrial process.

So with that, who would like to lead off?

And also I might say, I don't have a problem if you want to divvy up the arguments. You may have decided to do that, and I don't have any problem with that; but I would ask you, because we're not going through the appearances, for the court reporter, even though she knows all of you well too now, to

just before you begin, identify yourself if you haven't spoken before this morning.

So with that, who would like to begin for the plaintiffs?

MR. CORY: Good morning, Your Honor.

THE COURT: Good morning, Mr. Cory.

CLOSING ARGUMENT

MR. CORY: Good morning. This is Ernie Cory for the plaintiffs.

Your Honor, I remember your words last Thursday, and I hope that these remarks will crystallize some of the testimony you heard last week and hopefully will help you make the decision going forward a little easy.

I want to begin, Your Honor, with some guidance from the Ninth Circuit about the admissibility of expert testimony, and I bring your attention to Slide Number 2 where the Ninth Circuit has said when considering whether -- your job is to consider whether the techniques or the theories employed by the experts is generally accepted in the scientific community.

Secondly, Your Honor, the court said -- the Ninth Circuit has defined your task is to not to analyze the experts -- what the experts say but what the basis is for what they're saying.

And, lastly, Your Honor, Rule 702 as applied in the Ninth Circuit is that your job is to give a liberal thrust in favoring admissibility.

I thought those -- applied together, the plaintiffs have

met those thresholds for moving forward with trials.

Next, Your Honor, I want to talk to you a little bit about what the Seventh Circuit has said about the qualifications for experts to testify. We've got --

THE COURT: The Seventh Circuit you said?

MR. CORY: Sir?

THE COURT: You said the Seventh Circuit?

MR. CORY: Yes,sir. I mean, Rule 702. Excuse me.

THE COURT: That's a fine circuit, but --

MR. CORY: I know. They would have taken you to the Seventh Circuit. I'm going to stick with Rule 702 in the Ninth Circuit.

THE COURT: All right.

MR. CORY: Thank you, Your Honor, for correcting me.

Rule 702, let's stick with that.

The next slide, Slide 5, is our experts, and the first question is: Are they qualified? Do they meet the criteria?

The defendants are not disputing the qualifications of a single one of our experts. They are all board-certified -- all the physicians are board-certified in their area of specialty and the rest of them are Ph.Ds. They have offered opinions within their area of expertise. Not a single expert in this case, Your Honor, has stepped outside of their lane. And so as to their qualifications and trainings, Your Honor, it is the plaintiffs' position that all six experts meet the

qualification criteria.

The next criteria is data and the question is the sufficiency of the data. We don't have those binders here today, but as respect to the sufficiency of the data, that's an easy question for the Court to decide.

Both sides together stipulated and included the entire body of evidence to be considered. There it is right behind you. There's not a study or a paper -- I think we have some additional papers but, for the most part, all the papers and all the studies are right behind you; and so as to the sufficiency of the evidence, that's not in dispute. So with respect to the data, we say the answer as to all six of our experts is yes.

The third criteria is whether the testimony is a product of reliable methodology. This case primarily relies on epidemiology and biological plausibility. With respect to the epidemiologists, they considered the totality of the epidemiological studies and performed an in-depth Bradford Hill analysis, which is the acceptable methodology in the Ninth Circuit. As to our biological plausibility experts, they considered the totality of the evidence, including the purported anticancer effects of PDE5 inhibitors in forming their opinion.

So with respect to the methodology employed, it is the plaintiffs' position, Your Honor, that all six of the

plaintiffs' experts meet that criteria and should be able to move forward.

The last criteria is the methodology -- is whether the methodology has been reasonably applied. All the experts have reviewed and analyzed the totality of the evidence. They did -- plaintiffs' experts. They did not cherrypick. They weighed the evidence appropriately, and they explained their conclusions in their reports, in their depositions, and in their testimony.

You're going to hear more about this criteria from Munir, but as to whether or not they meet the criteria for reliability, Your Honor, it is the plaintiffs' position the answer is yes.

THE COURT: Let me give you an opportunity to respond to something that came up right at the beginning, I think, of the discussion last week. And I think it was Mr. Petrosinelli made some reference to Mr. Piazza and said, well, that was the plaintiffs' signature expert and apparently styles himself as being quite the expert in the relevant field, but because he has a patent and that patent in part talks about PDE5 inhibitors as possibly having beneficial effects for cancer treatment, that, therefore, that's one witness you decided not to present, suggesting that somehow he would be no longer helpful to you. I wanted to give you an opportunity to respond to that.

MR. CORY: We would have liked to bring all six experts. We had eight hours, number one.

Number two is that we had to make our case against both defendants, and we needed an epidemiologist and a biologically plausible expert as to both defendants. Dr. Piazza, we couldn't fit him into the equation of how to be here --

THE COURT: Right.

MR. CORY: -- and so we --

THE COURT: Well, and that's -- I think your decision on which of your experts to present isn't really the basic point. The basic point was: Is he now problematic for you because he has this patent?

MR. CORY: Not at all, Your Honor. As a matter of fact, that's another red herring. His patent is on PDE5 -- PDE10. It is not on PDE5.

THE COURT: That's true, but they showed me there was a reference in I think it was the specification that made reference to the fact that, indeed, in addition to -- I know it was PDE10, but it made reference to the fact that PDE5 inhibitor, a medication could be theoretically helpful for cancer treatment.

MR. CORY: And, once again, I'm not a patent lawyer and I don't want to be when I grow up, but I do know that from what we understand in the world of patents, you try to cover as many bases as you can and you try to put in as many things as

you can so that no one else can come in and try to usurp your patent. That was one of the explanations that was explained by Dr. Piazza.

And number two was, is, as he said before, all he was doing was taking some information that was published in the peer-reviewed literature and including that in his patent.

No, it is not problematic; no, Dr. Piazza would be here; and, no, we stand by Dr. Piazza and we do not think that patent is an issue in this case.

Okay?

THE COURT: Okay.

MR. CORY: What I'd like to do -- if you think about it, Your Honor, from reading some of the defendants' briefings, the defendants want to run to the Second Circuit and they want you to rely and use that law to dictate the case -- to dictate the ruling in this case. They want to run away from the Ninth Circuit or cherrypick cases from the Ninth Circuit.

The last thing they want you to ever do is to consider -- and I hope I'm pronouncing it right -- Judge Chhabria -- is that close?

THE COURT: Judge Chhabria, right.

MR. CORY: Okay.

-- the last thing they want you to do is consider his ruling in --

THE COURT: In Monsanto?

MR. CORY: -- in Monsanto. They don't want to talk about that.

What I would like to do, if you would, Your Honor, is let's look at our case in light of that ruling, and I call your attention to Slide 6.

In that case, Your Honor, the Court found that the plaintiffs presented -- I'm going to paraphrase this for you -- the Court found that the plaintiffs' presentation on a causal link seemed rather weak, some of the epidemiology studies showed to be slight or moderately associated with an increased odds, and the largest and the most recent study suggested no link at all. That was the epidemiological evidence in that case.

And what did the Court do with that? They entered the following order (reading):

> "The plaintiffs' presentation at this phase is not whether or not the plaintiffs' experts are right. The question is whether they've offered opinions that would be admissible at a jury trial; and the case law, particularly in the Ninth Circuit, emphasized that a trial judge should not exclude an expert opinion."

I'm just reading the order, and I know that's probably something you can do yourself. Would you rather me not?

THE COURT: No, no. Well, I can tell all of you, because it will come as no surprise, that I will look at

Judge Chhabria's order with some care. He's my next-door neighbor and good friend I might mention, and I have a great deal of respect for both how much work he put into that and his just general abilities; but he'd be the first to tell you that he's another district judge, not binding on me --

MR. CORY: I understand that.

THE COURT: -- only as good as the persuasive force of the opinion just like anything I write is vis-a-vis him.

So I will look at it, and I'm very aware of it, of its existence; but if there are things in his opinion that you want to highlight, I don't want to stop you from doing so because I do have enormous respect for him. So, you know --

MR. CORY: The only thing I would add -- I don't mean to cut you off, Your Honor -- was that it is his opinion that there was enough scientific evidence to not preclude a jury trial.

And it is plaintiffs' position in this case that we have better epidemiology and better biological plausibility literature than there was at the Roundup -- in the Roundup case at the time that the judge entered his ruling in that case.

Your Honor, the role of PDE5 -- the role of PDEs in melanoma has been established long before the Arozarena article was published; but in 2011 and in 2016, two peer-reviewed studies that you're well aware of by now were published. Those both conducted cell studies and animal studies to study the

effect of melanoma progression.

Let's talk about the Arozarena paper. You heard our experts' opinions on the study. No matter how much money they paid Dr. Marais or his lab, the one thing you did not ever hear him -- we do know is he has never publicly disputed one word of that paper. He has sat in this courtroom and stood by his paper. And the only place in the world where that paper isn't good law is in the four walls of this courtroom -- I mean, good science, is in the four walls of this courtroom.

THE COURT: Well, their point, though, is not to run away from the paper but to say you're misinterpreting it, and then they point out that he's one of the grand formulators of it and he says it doesn't mean what you say it means.

MR. CORY: And, Your Honor, assuming that that is what he said, doesn't that go to the jury? Doesn't it go to the jury? You're right. I'm right -- you're wrong. I'm right. You misinterpreted it. Let the jury decide.

THE COURT: But what is the -- you have a study's author and the study's author gets on the stand and said, "This is what myself and my colleagues meant by this study," what -- just -- it can't be enough for you to just get up there and say, "We don't believe him and we read this study and we think it means something else." What's your countervailing -- you have to have some countervailing reason to disbelieve that testimony.

MR. CORY: Absolutely, Your Honor.

THE COURT: And that would be?

MR. CORY: The first author of that study, Dr. Arozarena, who as late as 2017, if you'll look at the slide, in 2017 Dr. Arozarena and Dr. Wellbrock published exactly the mechanism that we're proposing in our arguments. Not only that, they went on to talk about the Li study. So he's not the only man in the world that -- the first author of that study disagrees with him.

And let's talk about the Dhayade paper. It was a sophisticated study that used generally accepted scientific methods and it came to a conclusion that they just -- the defendants, frankly, just didn't like. And so what did they do? Were they worried that this might be affecting men? No. They went out and hired experts to beat up the study and to criticize the study.

And so you heard from Dr. Ganesan and Dr. Haq, and they offered their opinions about each and every criticism lodged by the defendants, and that testimony should go to a jury. Just because they disagree about the paper doesn't exclude the paper and it does not exclude their testimony.

I want to talk a minute about epidemiology, Your Honor. There is no dispute from all the epidemiology studies that we've -- from all the epidemiologists that testified that a prospective cohort study is the best study of all. We got

that. That's the number one.

There's no dispute that if you're going to do an epidemiology on melanoma, you need to account for sun exposure. Of all the epidemiology papers that are introduced in this case, all those ones behind you, there was only one, the Li study, and the Li study had a finding of 1.84 statistically significant hazard ratio. The one study. I'm not calling it the gold standard, but the best study.

Once again, the findings of the epidemiology studies introduced in our case we claim are much, much better than the epidemiology studies that were submitted in the Roundup proceedings and that the jury should be allowed to interpret those findings.

Lastly, Your Honor, I want to talk about the biggest red herring in this whole proceeding, and that's the anticancer publications.

You know, what's interesting about that, everybody wants a cure for cancer. We all do. But it's interesting that neither Lilly nor Pfizer, the two biggest manufacturers of PDE5 inhibitors, are using -- are studying PDE5 inhibitors for cancer.

The deposition testimony of their witnesses is very, very clear that neither company is doing -- has any planned studies or has anything in the works to study PDE5 inhibitors for the treatment of cancer. I think that answers the question. If

Lilly and Pfizer don't care about it, it must not be there.

THE COURT: Well, do you think it's fair to really say that if those pharmaceutical companies aren't doing that particular study, we can derive from that the conclusion that they have come to some determination that it's -- they're doing all sorts of things, and I don't think it's tantamount to an admission on their part that they don't think there's anything to it simply because they're not studying it.

MR. CORY: I agree with that, Your Honor, but I'm just having fun arguing. It sounds good for me.

THE COURT: Oh, no, that's fine. That's fine.

MR. CORY: Pfizer's anticancer expert, who they didn't bring to testify, Dr. Califano, who lives in South California, published a peer-reviewed paper that's in the material you have. In that paper he says that he -- they do not propose the use of PDE5 inhibitors as a stand-alone therapy for cancer. He published it, their expert.

As Dr. Ganesan said in his testimony, the publications fall into three buckets: Other PDE5s, other cancers, or for the treatment of late-stage cancer in combination with other drugs. That's it. It's irrelevant. It is the red herring in this case.

THE COURT: Do you also think it's a red herring when the defendants say, well, there's no indication that any of your experts, or certainly their experts, who do clinical

practice, and we heard many of -- several of them, that none of them seem to be in the mode of warning their patients about PDE5 inhibitors, those patients that have melanoma?

MR. CORY: Well, I think both of the plaintiffs' experts, Dr. Ganesan and Dr. Haq, testified that they did.

THE COURT: Well, what they sort of testified to is in their, if I recall correctly, in their general review of the medical history of their patients, they ask what medications they take and that, in their mind, would include a PDE5 inhibitor; but I didn't hear them say, "And if the answer to that is yes, we counsel them and spend time with them and tell them that, you know, these are the risks." I didn't hear them say that. I'll go back and look, but I didn't hear them say it.

MR. CORY: I think we'll find that testimony because I'm pretty sure they did say -- both of them did address it --

THE COURT: Okay.

MR. CORY: -- to the extent they've even had a patient that had it.

THE COURT: Well, it could be. I know that Dr. Schuchter, I guess, who was a defense witness, she said she did have patients that have that, and she said she didn't; but that's their witness, not yours, and I understand.

MR. CORY: Let's talk about the defense case. For three days, Your Honor, four experts sat on those benches back

there making thousands of dollars an hour, thousands. They've been hired guns for the defendant --

THE COURT: Both sides' experts were making thousands of dollars.

MR. CORY: No, none of ours. Well, Dr. -- I don't --

THE COURT: They may be making less than yours.

MR. CORY: Yeah.

THE COURT: I don't know what I take from that. I mean, they're all paid experts is the bottom line.

MR. CORY: We didn't get into Dr. Bastian agreed to work for us for 750, then he jumped there right to 1250.

THE COURT: That was the subject of motion practice.

I don't want to be flip about this, but my point is -- and I thought I kind of sent the message on this before -- I'm not naive about this process. There are paid experts on both sides. And when the argument is, well, this expert is being paid and, therefore, you should view them as an industry shill or a plaintiffs' shill or something, I know when we get to -- if we get to jury trial on some of these, legitimately there will be some discussion about the witnesses being paid and does that affect their testimony.

And I have no suggestion that's improper testimony; but I am not going to rule in this case at this juncture that any of these witnesses are somehow disabled because they're paid experts. They're all paid experts.

MR. CORY: Well --

THE COURT: And if they pay them more than you pay them, you know, maybe the jury will find that of considerable consequence; but, candidly, Mr. Cory, I think there are more substantive issues about these experts than how much they're getting paid.

MR. CORY: I'm going to get to them.

For less money than they paid those guys to sit in this courtroom last week, they could have done the tests.

THE COURT: Well, I don't know about that.

MR. CORY: They could have done the tests and performed the experiments to test this drug, but they didn't do it. Instead of doing the tests to protect the men, they chose to have experts -- they chose to pay these scientists to be expert witnesses, and I'm going to throw the question out there. What are they afraid of?

But I want to talk to you a minute about epidemiology and some of the meta-analyses that I question the quality of the science and whether -- and question how you should move forward with those studies in your analysis of this case. Some of those studies, quite frankly, are not as lily white as they appear.

Do you like that, Mike?

MR. IMBROSCIO: I didn't hear what you said, honestly.

MR. CORY: Some of those studies are not lily white.

I made that up myself.

Some look downright shady, Your Honor.

I want to talk to you a minute because it is easy in an epidemiology study to manipulate data. You've seen that. You've seen how the data has gone all over the place. It's easy to figure out who to select in a study and who to exclude in a study, what types of melanoma to include in a study, how many years after diagnosis to include it in a study, what the dosing is, are we going to put it in the study or are we going to leave it out of the study, the study groups, and an inclusion/exclusion criteria. The raw data comes and then the scientists have an opportunity to put together their study.

And I want to talk to you about a study in particular, the Loeb study, the 2015 Loeb study. I don't think you -- we can talk about money, but I don't think you can disregard the fact that at the time that study was published, one of the writers was being paid fees by Pfizer and the second, Dr. Loeb, was being paid by Sanofi, which had a contract with Lilly to sell Cialis in Europe. There's no dispute about that, but --

THE COURT: Right. And I didn't mean to suggest in my comments -- there's a difference between the studies themselves being sponsored by industry and the effect on analyzing the studies and expert witnesses testifying in a case.

And I wasn't suggesting that because -- that I didn't think when I said, "Well, how much these experts in my

courtroom are being paid is of critical importance to me," I wasn't suggesting "And that also doesn't mean that I care about who's funding the studies." I think that's a different proposition.

MR. CORY: Well, I want you to look at what's on the screen. It's clear that in the first Loeb study, Your Honor -- in the first Loeb study, there's the disclosure, Dr. Loeb and Dr. Lambe. I hope that's how you pronounce it.

But you know what? Lilly wasn't satisfied with that study so Loeb did a meta-analysis in 2017. You heard about it. She did that study, Your Honor, in 2017 after in 2016 being hired by Mike.

Where's that slide? There's the slide.

She's been hired in this case, and she was hired by a predecessor firm as far back as June of 2016 for $750 an hour plus all these extras to testify in this case. But did she put that in her meta-analysis? Is that a conflict of interest that should have been disclosed in the meta-analysis, Your Honor? Absolutely, and she didn't do it.

But if you paid attention to that meta-analysis, it had so many mistakes. My question is: Was it written by lawyers? It was a made-for-*Daubert* publication. It even had a Bradford Hill analysis.

THE COURT: Well, how critical is the Loeb study to their argument? I mean, it doesn't rise or fall --

MR. CORY: It's the perfect meta-analysis for Bradford Hill. That's the only -- of all the meta-analyses published, it's the only one with the Bradford Hill.

THE COURT: But my question is that I didn't hear that -- they certainly presented to me it's one of the studies, but I didn't hear them particularly emphasizing it to me.

MR. CORY: Well, maybe because they knew I was going to shove this piece of paper in their face; but it's there, Your Honor, and the entire scientific community has it.

And so they cleaned it up. They finally got -- you know, they knew the mistakes were there. They knew we knew that she had been hired by Lilly. So in August of 2017, she published -- how do you pronounce that? -- a correction.

And in the "Notes" section -- you notice where she hid it. She hid it in the "Notes" section. She did not disclose it in the "Conflict." She hid it in the "Notes" section that she was a consultant for Lilly.

So the question I have for you, Your Honor, is: What do you do with those publications going forward in your analysis of this case? It is clearly not unbiased science.

Now, Lilly is not the only one that was cooking the epidemiology in this case. Pfizer was too. The Pottegard paper in 2016, Your Honor, it's no surprise that the Pottegard paper is the worst paper for the plaintiffs in this case. I submit to you it's not an accident.

Plaintiffs were exchanging e-mails -- Pfizer was, excuse me -- I said plaintiffs -- Pfizer was exchanging e-mails with one of the study authors of the Pottegard paper two years before it was published. They produced those e-mails. They even flew -- the deposition testimony is they even flew one of the study authors to New York to make a presentation that they say was not about Viagra.

We can't verify it because we were very limited in our discovery, but what we do know is this: One of the study authors, Dr. Sorensen, was paid over $90,000 in personal grants from Pfizer in 2016. I know that if we're allowed to move forward -- once we've been allowed to move forward, we'll get to the bottom of this.

THE COURT: Isn't there, though, some tension between your argument that the pharmaceutical companies shouldn't be spending their money on experts in this case, they ought to be spending their money doing some of these studies, and then at the same time saying it's outrageous that they're spending their money to fund some of these purported studies? I mean, you can't have it both ways, can you?

MR. CORY: But you have to look at the study, Your Honor. They're cooking the books.

THE COURT: Well, and your conclusion is because they're spending the money. Well --

MR. CORY: But you know what? I'd be okay with the

Pottegard study. I would discount the Pottegard study if, in fact, there was a disclosure in the study. We would all look at the -- we would look at these studies differently if we knew that they were being funded by industry.

THE COURT: So they're hiding the funding is what you're saying?

MR. CORY: Well, clearly they hid it in -- well, it wasn't disclosed in Pottegard. We haven't got to the bottom -- I mean, we haven't gotten to the bottom of it. We still have work to do. We know they didn't disclose it in Loeb until six months after the second study, I mean, when she was finally forced to correct her mistakes. And you just look at the data.

So let's talk about the defense experts because I want to sit down. I've burned up my time. Yeah, I burned up my time.

THE COURT: Your colleagues won't be happy with you there, but go ahead.

MR. CORY: Your Honor, there they are, and each and every one of them is a qualified expert within their area of expertise. Each and every one of them.

But let's talk about Dr. Schuchter, for example. Her report is very clear. I took her deposition, a very nice lady. She deferred -- in her deposition she defers to the biological mechanism people for the mechanism. She just defers.

And she is not an epidemiologist. She's not studied epidemiology. She didn't do a Bradford Hill analysis. Is it

the law of the Ninth Circuit that any physician can opine about epidemiology and a causal association? Because if it is, then that means all four of our -- that means Dr. Haq and Dr. Ganesan, they're just as qualified as Dr. Schuchter is to offer causality assessments.

So the answer to the question about Dr. Schuchter is, well, yes. Yes, she is qualified but, no, she's not qualified to give biological plausibility opinions nor is she qualified to give epidemiological opinions. So, yes, she can talk about melanoma and I guess she can talk about what she tells her patients, but what does that have to do with a *Daubert* hearing?

And let's talk about Dr. Marais. Absolutely qualified, yes. Beyond qualified, him and Einstein, but he applies the wrong study. He says you've got to prove it in men -- in humans to have biological plausibility. That's what he testified to.

The same with Dr. Bastian. He gave a causality assessment. He's not qualified to. And he used the wrong standard. But is he a qualified scientist? Absolutely.

Now, they want to talk about Dr. Witte. We didn't file a motion on Dr. Witte. He is absolutely qualified to talk about epidemiology. We absolutely -- we disagree with it, but he stayed in his lane. We were not going to waste your time or their time to talk about an expert who is qualified and stayed in his lane.

So I'm going to end with this before I let Munir get up and take the rest of my time:

Based on the evidence from all of our six experts, Your Honor, in the law of the Ninth Circuit, we've answered your question that you raised last Thursday. We should move forward with the trial by jury.

Thank you, Your Honor.

THE COURT: Thank you.

CLOSING ARGUMENT

MR. MEGHJEE: Thank you, Your Honor. Munir Meghjee from Robins Kaplan on behalf of the plaintiffs.

To follow-up, Dr. Ahmed was asked in her cross-examination about talking with her patients. And she said at the time of her deposition, she didn't recall any patients that were taking PDE5 inhibitors that she was treating for melanoma; but since her deposition, there was a male patient who was prescribed a PDE5 inhibitor she was treating for melanoma and she did warn him of the risk -- warn him of the association that's been found in the literature. And I believe that's at 428 of the transcript, if my memory serves me correct, just to follow-up on that.

THE COURT: Okay.

MR. MEGHJEE: And if you would like to hear more about Dr. Piazza, I think Ms. Miller can address his testimony in particular.

THE COURT: No. I think we've exhausted that subject.

MR. MEGHJEE: I'll try not to repeat too much of what Mr. Cory did. I really would like to focus on what Mr. Petrosinelli said in the opening statement, that the dispute here is about Rule 702(d), the expert has reliably applied the principles and methods to the facts of the case.

And they've made a few arguments on this particular piece. The first is, and this is what I'd like to discuss, the first is they say, well, our experts improperly have applied the methodology; and then they say that because their conclusions, according to the defendants, are not generally accepted, therefore, they must have improperly applied the methodology. And I'd like to break both those arguments down if I could.

Let me begin, though, with this: The Ninth Circuit has made this point very clear, that your task, Your Honor, is not to judge the correctness of the experts' conclusions, who's right or who's wrong, but the soundness of their methodology. It's the fact finder that must decide how much weight to give that testimony based on cross-examination, contrary evidence, and proper instruction on the standard of proof.

So let me start now by talking about our mechanism experts and the methodology they used, Drs. Haq and Ganesan. Defendants' argument is that they improperly extrapolated their conclusions from the data in the Arozarena and Dhayade studies and ignored the anticancer literature.

They both testified, Your Honor, that they considered and critically evaluated the Arozarena and Dhayade studies. They critically evaluated what the cell studies showed and what the mouse study in Arozarena, Figure 7K, and Dhayade, Figure 6, what that showed, and they addressed the strengths and the weaknesses of those experiments. They critically evaluated it so it's not a situation where the defendants are making up their opinions out of whole cloth unsupported by the studies.

Now, they acknowledge the findings of Figure 7K. They critically assessed it. They interpreted that data in connection with the other data in Arozarena, and they reached their conclusions.

You heard Dr. Marais testify about the role of cell studies, animal studies, in investigating signal -- I can't remember the words he used -- I think cellular transduction signaling in melanoma progression. It's perfectly appropriate to rely on cell and animal studies for biological plausibility.

And the jury here is not going to be deciding whether the dose in Arozarena 7K was right or wrong or whether the dosing in the Dhayade mouse study was right or wrong. What they're going to be assessing is whether on the entire body of evidence should the opinions of the experts be credible.

You know, the *Reference Manual On Scientific Evidence*, we cited this in our briefs, cautions against the atomization of evidence as you make your *Daubert* inquiry. The test -- you

must consider and the experts should consider all of the relevant scientific evidence taken as a whole to determine whether their conclusion is supported, not atomize the evidence.

THE COURT: Well, that's the ultimate task of the fact finder to make that determination; but I can't say, for example, well, I think this particular study that's being offered has so many defects, it doesn't pass the threshold; but because there's other evidence in there, I'm going to let it be included in the hopper. I can't do that.

So this holistic concept, which I don't disagree with you is how ultimately the fact finder has to look at something, is not my *Daubert* responsibility. My *Daubert* responsibility is to be, I think, specifically looking at each of these offered experts and determining whether or not they have a basis to be part of the hopper, isn't it?

MR. MEGHJEE: Well, I agree with that, Your Honor.

THE COURT: So it's not a holistic, let me take all that you've offered and, okay, well, there's strengths and weaknesses but there's a lot of other evidence so I'm going to throw it in there. I can't do that.

MR. MEGHJEE: And that's certainly not what I'm arguing.

THE COURT: Okay.

MR. MEGHJEE: What I'm arguing is about Dr. Haq's

analysis of all the data, and he has analyzed all the data and he has considered the data that they claim is unreliable, the Dhayade study, and he's evaluated that data amongst all the data. That's what I'm referring to.

And I will point out that -- and you asked this question of Dr. Haq, "Are you alone in this theory?" And I think we've shown you the evidence that that's not the case. We showed you the series of quotes out of the epidemiological studies where they all point back to the Arozarena study as establishing a plausible biological mechanism.

I understand that's epidemiologists, but if -- go to Slide 2, please.

And that's what Li and his co-authors say and they're discussing Arozarena. This is what led to the Li epidemiological study. (reading)

"Given that PDE5A downregulation increased invasiveness and it was higher in primary tumors than in metastatic tumors, it's biologically plausible..."

But a similar --

THE COURT: Can I ask you just a very specific question?

MR. MEGHJEE: Yes.

THE COURT: As I was reading through the transcript the last couple days, I don't think anyone ever explained to me when the alphabetical ending, the A and then sometimes it will

be different, what is that?

MR. MEGHJEE: I don't think I'm prepared to answer that question, Your Honor. I'm not sure either.

THE COURT: Okay.

MR. MEGHJEE: PDE5 -- I just -- PDE5A is the enzyme. Perhaps one of my colleagues can --

THE COURT: Sometimes it's a different alphabetic ending, which is why I ask, I think. Sometimes it's got an "I" in there.

MR. TATTING: If I may, Your Honor --

THE COURT: Yes, go ahead.

MR. TATTING: -- there's a few different ways.

Your Honor, I'm sure they've got an opinion on this too, but there's PDE5A and there's PDE5B, but we're talking specifically about a PDE5A inhibitor. Sometimes they shorten that just to say a PDE5 inhibitor.

THE COURT: That's right.

MR. TATTING: And then other times they'll say a PDE5i, which essentially just means PDE5 inhibitor. So the "I" would stand for inhibitor. Like we use PDE5i's. That's essentially shorthand for saying we use PDE5 inhibitors.

THE COURT: Is it fair to say I can just ignore the alphabetic ending on the PDE5 when I see it?

MR. TATTING: I would say for the most part with the A, yes.

THE COURT: Okay. You-all agree on the defense side?

MR. PETROSINELLI: The A is a phenotype of that particular enzyme and it is the phenotype that these inhibitors work on. So it's the relevant PDE5A.

THE COURT: Okay. Very good.

MR. MEGHJEE: Thank you, Mr. Petrosinelli.

THE COURT: Go back. I'm sorry I diverted you on that, but I was curious. Go ahead.

MR. MEGHJEE: And I don't want to spend -- you know, this conclusion is shared by, for example, the Pottegard authors in Slide 3 and the Tang authors in Slide 4.

And you heard Mr. Cory discuss Dr. Arozarena's conclusion in his 2017 article, and we'll be submitting that. I think that's -- I'm not sure if it's in there as a joint exhibit or we'll need to submit it to you as one of the extra exhibits, but we'll work on that with the Court.

But other scientists as well, not just epidemiologists, and Dr. Arozarena, have recognized this in the science. And I cite to the Court Joint Exhibit 107, and I don't have a slide for this but it is a joint exhibit. It's referenced in the briefing. It's the commentary by Dr. Housley, and Dr. Housley, first he submitted a companion commentary with the Arozarena paper in 2011. That's Joint Exhibit 106. And then sometime after the Dhayade paper, he submitted another commentary about these two studies, and that's Joint Exhibit 107.

And Dr. Housley in those commentaries, and especially in Joint Exhibit 107, he characterized the Arozarena and Dhayade studies as releasing the break on proliferation and metastasis of melanoma provided by PDE5.

So they're not alone in their assessment of biological plausibility. They're not alone in their assessment of the Dhayade study as a reliable basis on which to base their opinions notwithstanding the weaknesses of the experiments and the way they were conducted.

And both Dr. Haq and Dr. Ganesan recognized that and acknowledged that. Dr. Haq said it's not as robust as the Arozarena study. The science isn't perfect, but it's enough for them not just to opine that they passed that threshold of possibility but that they can opine on the biological plausibility to a reasonable degree of scientific and medical certainty, and that conclusion can be tested before the jury.

Let me turn to causation experts, and I want to -- I may go through --

THE COURT: Let me just ask before you leave the Dhayade study.

MR. MEGHJEE: Yes.

THE COURT: The biggest issue seemed to be, they may tell me this isn't the biggest issue, but this point that the study used is B16 cell line, that 75 percent of the mutations that cause melanoma are not included within the cell line

effectively that's being used in the study; and that, therefore, if it's 75 percent effectively not being included in this, what's the value of the study?

That's effectively what I heard them saying. It's probably a simplistic characterization of their argument, but I think that's what they were saying.

You're saying your experts acknowledge that it's not a robust study. I think they were being a bit stronger than that and saying it's just not a study that we can use in this context. So tell me why they're wrong about that.

MR. MEGHJEE: Well, on the B16 mouse model, a few things about it. I mean, Dr. Haq I feel addressed this in his --

THE COURT: Remind me what he said about it.

MR. MEGHJEE: -- cross-examination and in his direct examination. It's not a perfect model but you use it because it's immunocompetent, and what this study is testing is the activation of this molecular pathway.

And there's a number -- and Dr. Haq said -- you know, I didn't even go through all of that in his direct, but there's a number of other tests and experiments reported in the figures of Dhayade focusing on the activation of this particular pathway, and that's not impacted by the B16.

Now, it is just one cell line. He did point out, and Dr. Ganesan pointed out, that that's a commonly used cell line.

It's a cell line used in a lot of the immunotherapy treatments for melanoma. An individual -- I can't recall his name. I believe we cite it in the brief. A doctor did a number of studies on immunotherapy. He won the Nobel Prize a couple years ago, relied heavily on his experiments which used this B16 cell line.

So no cell line is going to be perfect and answer all questions, and it's one data point among many you use to reach the conclusion.

So there is no science that evaluates every single possible melanoma cell line, but you've got to take all the science put together and see if you can draw a conclusion.

THE COURT: Okay.

MR. MEGHJEE: Now, to the causation experts, Dr. Ahmed and Singh, first, they weighed all the data points in the epidemiology to assess whether or not there's a true association. And, you know, defendants tried to reduce the epidemiological data to the primary findings, and then they pick out the secondary findings for a different analysis on basal cell carcinoma. Here's a slide that they showed you in opening.

But I'd point out, Your Honor, that in examining all of the available epidemiological data -- and go to the next slide, please -- in these 10 epidemiological papers covering 11 studies, there's over 300 total reported risk ratios on PDE5

use and melanoma. Many of them are statistically significant. Many of them have risk ratios above 1.0 in the secondary analysis. There's all sorts of different analyses in that epidemiology besides that single point that they would like -- the defendants would like to take out and characterize as 1.12. That's the risk elevation if you look at it all together.

And, you know, on that point, though, on the 1.12, defendants argue, well, there can't be a true association because the relative risk is small; and I think we addressed that in the cross-examination of Dr. Schuchter, and I think Dr. Ahmed and Dr. Singh both addressed that. They gave the example of secondhand smoking on the next slide, please, and that the reported literature on secondhand smoking has a relatively low hazard ratio, and the same with UV exposure on Slide 8, please.

So just because there is a relatively low, in defendants' view, relative risk does not mean that there cannot be a true association, particularly when you're talking about cancer or acceleration of a disease, and we discuss this in our briefing and cite portions of the reference manual.

The other argument I'd just like to touch on briefly is basal cell carcinoma and --

THE COURT: Can you stop for one moment?

MR. MEGHJEE: Yes.

THE COURT: There was a lot of discussion about the

first Bradford Hill factor, the strength of association, when they were doing the analysis.

MR. MEGHJEE: Yes.

THE COURT: And this is where -- the reason why I wanted to bring it up now is when you make reference to the tobacco studies --

MR. MEGHJEE: Yes.

THE COURT: -- the tobacco situation. Tell me what you think the strength of association means when I'm looking at the Bradford Hill work that the experts did. Is it that even if it's a relatively low risk factor that's found, there are many studies that find the risk factor and, therefore, that is a strong strength of association; or is it that in the particular studies they find a big risk factor? Which is it from your perspective?

MR. MEGHJEE: From my perspective, it's across the body of epidemiological literature, and I want to stay with the consistency. You know, so I'm trying to separate out those two, but across the epidemiological studies they do report high risk factors.

And, you know, the strength --

THE COURT: Let me rephrase the question. Do you find a high strength of association if -- let's take in the tobacco situation you have 25 studies all finding some risk factor of about 1.2 or whatever. Is that a strong association or is it

that, well, we have three studies and each of them find, like the Li study, 1.84 or over 2, that's a high strength of association; or is it a combination of both?

MR. MEGHJEE: I think it's a combination of both. And one slide that I don't have is, you know, you can look across these studies and find a number of analyses with high associations, not just the 1.84 in Li. There's a number -- a number of these studies report in their secondary analyses, in particular subanalyses eliminating people with, you know, chronic health condition, or however they assess the data, that are 1.5, 1.6, 1.7.

So it's looking across all the studies and saying, yeah, there are relatively high numbers reported depending on how you look at the data. I'm not sure if that fully addresses your question.

THE COURT: Okay. Go ahead.

MR. MEGHJEE: I'll touch briefly on basal cell carcinoma.

THE COURT: I see you looking at the clock.

MR. MEGHJEE: I'm a little worried.

THE COURT: Don't worry about it.

MR. MEGHJEE: Mr. Cory told me I have 15 minutes so --

THE COURT: I actually want -- I want us to finish by lunch, but don't -- I mean, I want this -- I want you to have an opportunity to tell me why you're right, and so I'm not

going to cut you off at 10:00 o'clock or what have you. So don't worry.

MR. MEGHJEE: I'll take a breath and slow down --

THE COURT: Yeah, go ahead.

MR. MEGHJEE: -- in that case.

So the defendants say that there's an equally strong association shown in these epidemiological studies for basal cell carcinoma and, therefore, there can't be a true association with melanoma, and both Dr. Singh and Dr. Ahmed addressed this.

THE COURT: Because PDE5, everybody agrees, cannot be a trigger for basal cell carcinoma.

MR. MEGHJEE: Well --

THE COURT: That's the one thing everybody seems to agree on.

MR. MEGHJEE: I think our experts said they don't know of any science. They don't know if it's been studied.

THE COURT: Okay.

MR. MEGHJEE: They're not aware of that science. And I think one of the epidemiological studies, I believe it's Ma, specifically says that, you know, we should look at it. So I think we can all agree that no science has been presented in this courtroom, the experts haven't considered any science that would show that there is a mechanism.

But this is a matter of disagreement amongst the experts.

We didn't hear from Dr. Witte, but that's who would have presented it. It's a matter of disagreement from the experts.

You know, Dr. Ahmed pointed out that there's only one study which used a validated method to control for sun exposure, and that was the Li study.

These other studies that purport to use basal cell carcinoma as a negative control for melanoma risk, none of them cite any science for the support that basal cell carcinoma is a validated negative control for melanoma risk.

And she went through in her slides and pointed out how -- the studies that address basal cell carcinoma, how she weighed that because some were *post hoc* analyses, in other words, the studies weren't designed to look at that question; some were on the secondary analyses that the findings weren't consistent. So she addressed that.

Now, I understand they're going to say that but that is, in my mind, a quintessential issue to be tested on cross-examination in front of the jury because it's not established.

Those studies weren't designed to look at basal cell carcinoma, and the one study that looked at sun exposure, a control for sun exposure, had a significant difference, that's the Li study, in incidence of basal cell -- risk ratio for basal cell carcinoma and for melanoma.

Now let me turn to their application of Bradford Hill and

our experts' application of that. And I'd like to begin with what your colleague, Judge Chhabria, said in the Roundup litigation, and he acknowledged that it's subjective inquiry to a certain extent and that the experts will often disagree.

And so the analysis for the *Daubert* stage is whether the experts' methods were not so unreasonable scientific practice to be unhelpful or misleading to the jury, and they're not based on unreasonable extrapolations of the existing data. And you heard Mr. Cory talk about the underlying data in that case.

And the experts in that case, they focused, as our experts do here, on consistency, temporality, biological plausibility, strength of association in the studies that were controlling for confounders, even in that case where individual studies didn't particularly reflect a strong association or no association at all.

Our experts came in here and testified and they told you transparently how they weighed the evidence at hand. Dr. Ahmed testified about the weight she gave each Bradford Hill factor and why. Dr. Singh talked about how he balanced the strengths and weaknesses of the studies. And ultimately they both found that the consistency, strength of association, particularly in Li, the temporality demonstrated by the studies, the strong evidence of biological plausibility, you know, how those factors outweighed issues in the data regarding other factors that they openly addressed.

So here the experts considered the totality of the evidence, including the effects of bias and confounding, and they explained that to you. And if the defendants believe that that's weak, they can expose that in cross-examination. The jury is perfectly capable of understanding that.

And now I'd like to take the last few minutes to address what I think is the crux of defendants' argument, at least as it was laid out in opening, and that's they've asked you to exclude our opinions of our experts because the conclusions they say are not generally accepted of these causality experts.

And all this talk about general acceptance makes me feel as if I'm back arguing under *Frye* instead of under *Daubert*. So I want to break apart the law on what's meant in the cases that talk about general acceptance in the context of *Daubert* because in *Daubert* the court made clear that the focus must be on principles and methodology, not on the conclusions of the experts, and that's been reestablished and, you know, stated again and again in the Ninth Circuit.

And you've heard over and over how the defendants have said that, well, regulators don't agree that there's causation, study authors don't agree that there's causation; and, therefore, the conclusions aren't generally accepted.

Now, again, pointing to Roundup because it's right here, it's next-door and it's recent, the Monsanto case, Judge Chhabria addressed this issue, and this is how he

described it citing the Supreme Court's *GE vs. Joiner* case that defendants cite all over their brief (reading):

"The Court must consider whether, for a given conclusion, there's simply too great of an analytic gap between the data and opinion proffered."

And that stems from the *Joiner* case.

And if I could get the quote from the *Joiner* slide up, the next slide.

And here's what the Supreme Court said in *Joiner* (reading):

"Conclusions and methodology are not entirely distinct from one another. Trained experts commonly extrapolate from existing data, but nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A Court may conclude there's simply too great of an analytic gap."

So in *Joiner*, that case involved the exclusion of an expert who testified that a man's lung cancer was caused by PCB exposure, and that was based on two animal studies linked to a completely distinct type of benign tumor and four epidemiological studies, one of which didn't even study PCBs and one which studied a whole host of possible carcinogens. That's the *ipse dixit* of the expert, and that's not our case.

Now, the next slide, please.

The defendants put this up in their opening. It's a quote from *Nexium*, which is, in fact, actually quoting the Ninth Circuit *Lust vs. Merrill Dow* case.

And in *Lust*, the court said (reading):

> "When a scientist claims to rely on a method practiced by most scientists yet presents conclusions that are shared by no other scientists, the district court should be wary that the method has not been faithfully applied."

And that's where the defendants get their general acceptance argument.

In *Lust*, the purported expert wrote an article outside of his area of expertise after he'd been retained by plaintiffs' counsel but before he did his report. It wasn't peer reviewed and he couldn't demonstrate that the methodology he used in that article was generally accepted or espoused by a recognized minority. That's what led to that quote from *Lust* and that's the focus of the *Lust* and the *Nexium* case.

But here the actual methodology used by our experts is generally recognized as reliable. That's Bradford Hill.

So now let me turn to what they say factually because there's no requirement outside of this courtroom and their argument that others outside of this courtroom, including regulators or the medical community, must have found that

causation exists in order for a toxic tort case to go forward. There's no case that says that, and I want to return to that at the end. I'll circle back and talk about the Ninth Circuit's *Wendell* case, which discusses that very point.

So factually Your Honor asked about the FDA document, Defendants' Exhibit 98, and that's a document that they base this general acceptance argument on. Yes, well, what are you to do with it?

And you may remember that the defendants provided to us the first time they provided to you when they sent a letter in April of this year, ECF Number 920, and they said this is a document which we just got under the Freedom of Information Act request, and we want to raise preemption issues that this letter raises with you, and they never did that. They didn't raise those preemption issues.

They didn't do that because a month later in April of 2019, the United States Supreme Court decided the *Merck vs. Albrecht* case, and the Supreme Court explained that in order to meet the standard for preemption, that the defendant has to show by clear evidence that they provided the FDA with all material safety data; and, number two, that the FDA took action carrying the force of law to reject the very warning that they wanted to have -- proposed to have on the drug label. So that could be by, you know, notice in comment rule making, by formally rejecting a warning label, or another agency action

that has the force of law.

That's not what this document is. This document is a memo, an internal FDA memo, written in 2017 by two doctors in the Division of Bone, Reproductive, and Urological Products of the FDA, not a formal opinion by the FDA.

You know, they say they got it in response to a FOIA. I take them at their word, but it's a 2017 document that's after the end of our general causation discovery period so I don't know what else they got in response to the FOIA. I don't know what the defendants provided the FDA. I assume that's been produced. I don't know the full context of that. We'll get into discovery on that if we go on to the next stage.

And this document does not make a conclusion of causation. What these authors say is there isn't enough evidence for them to conclude what causality at that time, and they recommend the situation continue to be monitored.

And as Dr. Ahmed testified about this document, it's looking at a narrow slice of the data. It doesn't discuss the Dhayade paper. It doesn't discuss all the epidemiology. It's not looking at the totality of the evidence that the experts in this courtroom have examined.

And the experts considered it. You know, it came out after -- we provided it to them after the defendants gave it to us. They testified about this FDA document.

It's just another data point in consideration of their

testimony. If they'd like to cross-examine them on that document in front of the jury, then they can. But what's the jury to do with it? And, again, I'm going to go back to the Monsanto case.

And if we could put up Slide 15, please.

You know, this is the instruction given to the jury in the Monsanto case in the Phase I trial about regulatory agencies (reading):

> "Now, you've heard testimony of the regulatory agencies involved there. You should not defer to any such conclusions. They're not a substitute for your own independent assessment of the evidence presented in this case."

That's another data point for the fact finder in weighing the testimony of the experts, not as a basis to exclude the expert.

You know, other facts on general acceptance. And only five more minutes. I don't want to take up too much time. I'll try to keep it at that.

They argued in opening -- or they stated in opening that the evidence is going to show that the study authors disagree with our experts' conclusions, and they put up snippets of quotes from epidemiologists.

Now, an epidemiological study, Your Honor, is designed to assess association, not causation. That's explicit in the

Monsanto case. It's in the reference manual. The studies -- an individual epidemiological study is not designed to answer the question of causation. It's for association. And the existence of an association, that's what our experts testified to and that's what many of these authors of these epidemiological studies say that their studies show.

So, for example, in the Han meta-analysis on Slide 17, please (reading):

"Conclusion: PDE5 inhibitor use may be associated with significantly increased risk of melanoma."

Now, whether it's causative, that requires further investigation they concluded.

And same with the -- similarly with the Deng meta on Slide 18 (reading):

"Our analysis indeed proved a significant association."

That's what our experts are saying about the epidemiological evidence.

And even in the primary studies, in Slide 19, this is the slide that the defendants put up in their opening with these quotes from each epidemiological study saying, well, you can't conclude whether it's causative. But, you know, they didn't tell you that these studies also conclude -- many of them also conclude that there is a true association. And I'm not going to go through them all now.

I'd like to jump ahead to Slide 23, please.

They also -- defendants have also said, well, there's peer-reviewed literature, there is in the literature others who have done a Bradford Hill assessment and they've concluded no causation; and so, therefore, our experts' conclusions aren't generally accepted.

And, you know, Mr. Cory already talked about the Dr. Loeb meta-analysis which does a Bradford Hill.

They also point to Defendants' Exhibit 76 by Dr. Berwick, who we acknowledge is a superb, you know, cancer epidemiologist. In that one-page paper, they say that she does a Bradford Hill analysis. Well, she mentions some Bradford Hill criteria. She looks at I think it's eight or so references. She doesn't look at the full totality of the evidence that our experts have done here.

But what does she actually say? She says (reading):

"This association should be further investigated... There's a strong need for rigorous scientific investigation into the suggestion that the association is causal..."

That's what our experts have done. She says -- and then she goes on to say (reading):

""Until data emerges, it's best to advise all patients."

That's her conclusion and that's consistent with what our

experts are saying and that's where the science is heading.

You know, in the end of July of this year, July 30th, there was a new article that came out in a dermatology clinician journal. It's one of our supplemental exhibits, Exhibit 182.

If I may.

And I don't want to make too much out of this and go into it in too much detail, I mean, but, you know, this is dermatologists now being informed in a dermatology journal that PDE5 inhibitor use is a risk factor in melanoma. So, you know, this article, "What's new in melanoma," it discusses risk factors on the second page. First one is ultraviolet light, and then in the second column it talks about the new science on PDE5 inhibitor use.

So the science -- this is where the science is heading and we've shown you three abstracts -- the Boor abstract, the Ma abstract, the Nardone abstract -- and they're working their way through the peer-review process and we're hoping we'll see soon the published peer-reviewed epidemiology of the data report in those abstracts.

The science is heading towards causation. In the *Wendell* court -- and if you can put up -- in the *Wendell* case in the Ninth Circuit -- if you can put up Slide 28 -- the Ninth Circuit said (reading):

"Perhaps in some cases there will be a plethora of

peer-reviewed evidence that specifically shows causation. However, such literature is not required in each and every case. The first several victims of a new toxic tort should not be barred from having their day in court simply because the medical literature will eventually show the connection between the condition and the toxic substance has not yet been completed."

Now, our experts have surveyed the significant body of epidemiological literature, they've identified the statistically significant associations, they've considered all the data, they've given legitimate reasons for their causality assessment, and their opinions are bolstered by Drs. Haq and Ganesan on biological plausibility; and in the end, I'd respectfully ask that the Court admit their testimony before the jury.

THE COURT: Thank you.

Why don't we take a break between the two sides.

Let me just ask you on a housekeeping matter. The exhibits, the situation with the exhibits, are they -- no one was moving things in and I took from that that there was some agreement perhaps between the parties as to what the evidentiary record would look like. Is that true?

MR. MEGHJEE: Yes. I think the parties are going to engage in a discussion of what exhibits were referenced and then submit them to the Court to make sure that both the

demonstrative slides and the underlying exhibits are clearly in the record.

THE COURT: Okay. Good.

And you're going to be meeting and conferring on that and getting that to me -- well, when do you think the agreed record will be completed?

MR. MEGHJEE: I think this week we'll be meeting and conferring.

THE COURT: Okay.

MR. MEGHJEE: So hopefully by next week we'll have everything submitted to the Court.

THE COURT: Okay. Good.

All right. Let's just take a break and start up at 10:30.

(Recess taken at 10:16 a.m.)

(Proceedings resumed at 10:30 a.m.)

THE COURT: Back on the record.

Who is going to start? Mr. Petrosinelli.

And just so I know, are you going to be dividing it up? Am I also hearing from Mr. Imbroscio, or are you the man?

MR. PETROSINELLI: I am the man, although Mr. Imbroscio, I have to thank him again just for efficiency sake, because we have a lot of the same arguments, he has ceded his time to me. Although I think the way we left it was if there were some things that he wanted to say that I missed, he might pop in --

THE COURT: Okay.

MR. PETROSINELLI: -- but basically I would handle it, if that's okay with Your Honor.

THE COURT: Fine with me.

CLOSING ARGUMENT

MR. PETROSINELLI: Great, Your Honor.

Let me start by just thanking the plaintiffs' lawyers for their vigorous advocacy and their professionalism throughout the whole process. I joke with Mr. Meghjee that he and I are often on the same side of the V, and that gives me great comfort this is just a temporary lapse of judgment.

And Mr. Cory, you know, what can I say? He and I have been friends for a long time, and I'm glad he's back in the saddle and here.

THE COURT: As we all are.

MR. PETROSINELLI: So let me start, Your Honor, with some law.

So when Mr. Meghjee started, I thought we actually had some agreement on something, and then he kept going and it faded. But he was correct, and as I said in opening, that the way that we think of this case is it's a Rule 702(d) case, which is that the question is whether these experts, particularly the causation experts, because, as I said in my opening, if Dr. Singh and Dr. Ahmed don't survive, then there's nothing left, and so the question is whether they've reliably

applied the method that they used, and we'll talk about the method they used, to the facts of the case.

One interesting note is if you look at the Advisory Committee notes to this rule when it was amended to add subsection (d) in 2000, they cited *Lust*, the *Lust* case, which says, and they showed the slide and I show it here again, that if you purport to apply a method that is reliable but, yet, your conclusion is not something others in the field reach when they've studied it, which we have here in spades -- and I'll get to that in a second -- it's not dispositive. No one *Daubert* factor is dispositive, but it is a huge *Daubert* red flag; and that is the one --

THE COURT: Is it a red flag when the others that have studied it reach the determination that they can't draw a conclusion as opposed to circumstances where they draw a conclusion and say disproved?

MR. PETROSINELLI: I think it is a huge red flag. In the case of a causation analysis, when you have study authors and the FDA and others who have done Bradford Hill analyses and medical organizations which say, "We have reviewed this same body of evidence" -- you know, some of them maybe here and there didn't review a study or two because they're earlier in the process -- "and you cannot look at this data and find causation." Whether they say it's insufficient to find causation or it's unlikely to be causal, there's various

iterations you've seen, that is a huge *Daubert* red flag. They're looking at the same body of evidence that Dr. Singh and Dr. Ahmed are looking at.

And I don't think there's any dispute about it, that this case is what I called I think in opening a tailor-made *Daubert* case, by which I mean the factors that the Court looks to, they're not exclusive, but the main *Daubert* factors -- general acceptance, peer review, testing -- they fail all those factors. There's no dispute about it. They try to apply a method, and we'll talk about the method they apply to overcome that problem.

I would suggest to Your Honor there is not -- we have not been able to find a single case in the Ninth Circuit or in this court in which the experts' opinions failed all of the *Daubert* factors but were, nonetheless, admitted. I suppose it's theoretically possible. It could be --

THE COURT: Well, what happened -- I mean, we've heard a great deal about Monsanto and my good friend and colleague next-door. What about Monsanto?

MR. PETROSINELLI: Totally different case, and this is -- I mean, the one thing about *Daubert*, I think you appreciate this, Your Honor, is it's very fact specific; right? You have to look at -- you're not going to hear from us you should exclude their opinions here because look at this case and it's exactly like our case. They're all over the map. So

it's very fact specific.

But the second thing in the Monsanto/Roundup case is that they had some of the indicia of reliability in some of the *Daubert* factors, at least Judge Chhabria found as much. And the main -- I think to me the two main distinctions are these:

Number one, the plaintiffs' experts in Roundup/Monsanto were not relying on studies where the authors reached the opposite conclusion, where the study authors -- in fact, indeed, in Roundup one of the plaintiffs' experts peer reviewed his theory. He was one of the authors of the main study. So in Roundup you didn't have a situation where the plaintiffs' experts were saying "We rely on these five or six epi studies," and the authors of the study said, "You can't rely on my study for causation."

Secondly, I just mentioned it, the plaintiffs' expert, or one of them -- two of them actually, had submitted their theory to peer review. They had --

THE COURT: In Monsanto.

MR. PETROSINELLI: In Monsanto. That is a huge distinction, and we'll get to what happened here with Dr. Singh and Dr. Ahmed. We know it didn't happen here.

And, third --

THE COURT: Is there any law that -- I understand you made that argument and I understand that that's, I guess, the state of things in Roundup; but is there any legal authority

for the notion that in order to credit a witness in this type of circumstance, that witness needs to have submitted their findings for peer-review analysis?

MR. PETROSINELLI: Of course, it's not a requirement, but it's --

THE COURT: Well, is there anything that even suggests it's a factor?

MR. PETROSINELLI: Yes, actually. The *Daubert II* decision, the Ninth Circuit decision.

THE COURT: Okay.

MR. PETROSINELLI: Will you go to Slide 13, please. This is what the Ninth Circuit said in *Daubert II*.

THE COURT: I mean, certainly -- I don't want to suggest here that if they submitted it and it was rejected, it doesn't satisfy peer review. That would be a factor of consequence.

MR. PETROSINELLI: Of course.

THE COURT: So I'm not suggesting it isn't, but you're taking it to the next level and you're saying the actual affirmative act of submitting it for peer review or the absence of doing that is something I can take into account.

MR. PETROSINELLI: That is what the Ninth Circuit said in *Daubert II*, "The plaintiffs' experts have been unable or unwilling to" -- "that they have been unable and unwilling undermines their claim that their methods are grounded in

science."

And why is that? Because of what peer review is. In the peer-review process someone looks at the methodology you're using and how you're extrapolating if it's animal studies, how you're extrapolating -- or if it's epi data, how you're interpreting it, and they evaluate it. And as you just pointed out, some manuscripts get rejected.

The fact that they're unwilling to do it -- by the way, these are all heavily published authors; right? The fact that they do it in their normal everyday jobs and they didn't do it here is a huge *Daubert* red flag. It's not dispositive but it is a huge factor in support of exclusion of their testimony.

So to me, if we get back to -- Derek, let's go to Slide 4, please.

This is the quote just now from *Nexium*. *Nexium* happens to be -- I think I mentioned this to you in opening -- happens to be the most recent Ninth Circuit decision in a pharmaceutical MDL that addressed causation. That's this case from a couple years ago, and it echoes what *Lust* said. It's the same point we've been making.

And this is not a situation, Your Honor -- and this to me makes this case a lot different not only than Roundup but many other cases. It's not that the authors didn't address the issue. As we just talked about, you can go study after study, they use the word "cause." They don't use the word --

Mr. Meghjee I think said, I don't think correctly, that these epi studies were just looking at association. They are looking at association but then they went on to say, "What does this mean with respect to cause?" That's why epi studies are done.

And, of course, Your Honor, we have not only the epi studies but the meta-analyses. Meta-analyses are, of course, at a higher level of the hierarchy of scientific evidence.

I was reading one of Your Honor's *Daubert* decisions last night, the *Mullin's* case, where you made that point, that meta-analyses are a higher form of evidence precisely because you can never conclude causation, or only rarely, from one epi study. The point of a meta-analysis is to combine the studies. You get more power.

And look what the meta-analyses authors said about causation. Remains elusive. We can't draw a conclusion. They looked at the data and they said, "If you look at this collection of epidemiological studies, you cannot conclude causation." That is directly contrary to the opinions that Dr. Singh and Dr. Ahmed offered about the epidemiological literature.

There's case law on this actually in this court. These two cases, the *Carnegie Mellon* case and the *Jones* case, make this point, and I won't read the quotes; but if you have an expert, it's not just that they're not generally accepted,

that's true here, but that the studies they're relying on actually reach the opposite conclusion or a conclusion that is different from what the expert claims it is.

That is another huge *Daubert* red flag. I would commend to Your Honor Judge Illston's decision in *Carnegie Mellon* because it touches upon a lot of the issues we have in our case.

So this is the law. They fall right within the confines of this Ninth Circuit, Northern District of California, law about the conclusions that they have drawn from the body of data.

Now, we also have in this case something that I view as unusual. It's because this case has gone on for so long. We actually quite recently have these studies that actually not only look at the epi data like the meta-analyses do, but actually look at Bradford Hill criteria; and they find no evidence of causation, unlikely to be causal.

These are, you know -- these are independent authors. I'll put aside Mr. Cory's comments about bias and so on. These are independent folks. Marianne Berwick is one of the most well-known cancer epidemiologists in the world, and this is what she published.

Now, let's talk about the anticancer studies because I think they misunderstand what we used them for. We are not saying, we have never said, that PDE5 inhibitors have been shown to be effective in treating cancer. There's some

suggestions of that in the literature.

What these articles are used for here is to support the complete lack of general acceptance of their experts' theory and the analytical gap that Mr. Meghjee acknowledged is partly the role of the Court to look at.

They are studying in this Hassel clinical trial, which you heard about, two years ago, they're studying -- they're giving PDE5 inhibitors, in this case Cialis, to metastatic melanoma patients, people whose melanomas have progressed -- remember, their theory is progression -- have already progressed and they have not stopped progressing despite the best-available treatment.

You would never, never give someone a drug that causes melanoma to progress when you're trying to stop the progression of their melanoma. It would never -- if it were generally accepted, if it were even thought to be a possibility, you would never do it. This study is conducted at the University of Heidelberg in Germany, one of the top cancer centers in the world. It has to get ethics committee approval. That's what we're using the studies for.

THE COURT: If I recall correctly, you were drawing the distinction between circumstances in which a pharmaceutical might be experimented with for a different kind of cancer --

MR. PETROSINELLI: Correct. This is melanoma.

THE COURT: -- than when it's the exact same cancer.

MR. PETROSINELLI: That's exactly right. They have -- there are plenty of other studies with PDE5 inhibitors used in other cancers. We could argue about whether those are relevant here. I think they are; but just to try to focus the *Daubert* argument, there are studies in melanoma, in metastatic melanoma, in human beings. It would never happen.

THE COURT: In addition to this German study, are there others?

MR. PETROSINELLI: Yeah. There are clinical trials being enrolled. Now, none of them have been published yet, but this is the one that has been published in the peer-reviewed literature.

So the FDA document, you asked the question. Let me explain to the Court what this is because, with all respect, the description we got from the plaintiffs didn't do it justice.

What this is is, when this litigation started -- this was generated by this litigation. When this litigation started, because the lawsuits were filed, we, the pharmaceutical companies, had to report the lawsuits to the FDA as adverse events. And so what happened, the FDA saw a big spike in reports of adverse events, and they opened what's called, you see it referred to here, a tracked safety issue, which is the formal FDA way of saying "We're going to look at this."

This document from 2017, which -- and they are correct, we

got it -- we just submitted a FOIA request and got it. It's that simple. This document is a compilation put together by the Department of Urology, that's the department under which these drugs fall in the FDA, where they ask all of the divisions of the FDA whose scientists might have a say in the particular question being asked.

So you see here in the Table of Contents clinical data, that includes the epidemiology data; the Office of Surveillance in Epidemiology, the oncology folks, the toxicology folks. They asked them all independently, "Look at this literature and tell us what you think about whether there's a causal association here." And then this document synthesizes the analyses of all those groups into one document. So this is a 50-page, single-spaced document that synthesizes the analyses of four offices of the FDA -- four divisions of the FDA. That's what this is.

And what does it conclude? The data are insufficient to draw a conclusion that there's a causal association.

So what does that mean? We weren't using it for preemption. There was a talk about -- it could be used someday if we had to for preemption, but here the point is just it's another lack of general acceptance, lack of peer-review point, which is that when you give all of this information to a third party, and it's a lot of third parties here because they have all these offices, this is what the conclusion is. That's what

that document is.

And they haven't changed the label; right? If they had concluded that there was reasonable evidence of a causal association, which is what the FDA standard is, you change the label. And that's how we know, by the way, their view hasn't changed because it's 2019 and the label hasn't changed.

And this is just --

THE COURT: Are you suggesting, then, that this is to be treated more or less like another study? Are you saying there's something extra by virtue of it being a government regulatory agency --

MR. PETROSINELLI: No.

THE COURT: -- or no?

MR. PETROSINELLI: No, other than the fact that it is the regulatory agency that is responsible for ensuring drug safety. I mean, unlike, you know, some of these study authors, that's not their job. This is their job. Only to that extent.

THE COURT: Okay.

MR. PETROSINELLI: And, by the way, this was the culmination of years of study. In other words, in 2014 when the Li article came out, the EMA, which is the purple on the bottom, and the FDA, the blue on the top, they started studying this and they have issued reports that we have gotten from FOIA every single year since 2014; and you see all the way to the right that's the document we just looked at, the medical

authors review in July of 2017, and every single document has said what I just read.

Now, this is the quote I mentioned to you before, Your Honor. Peer review, what's the state of the evidence on peer review? Well, we know what the state of the evidence is, which is that here their four experts who testified, and I don't think it's -- there's no dispute about it, none of them have submitted their opinions and methodologies and the application of the methodologies to peer review.

And the discussion we just had, that's why it's relevant. If you don't submit it to peer review, it is not exposed to critical analysis that could expose unreliable methods. That's why it's relevant here.

And particularly relevant in this case because of the point I made before, the *Kumho Tire* case, which is sort of a third *Daubert* trilogy, one of the points it made is what we're really looking for is experts who do the same thing out in the real world that they come in the courtroom and they're doing. And what was the evidence on that with respect to, again, focusing on the causation experts, Dr. Ahmed and Dr. Singh?

Mr. Meghjee made reference to this. I don't know if you caught this in the testimony. Dr. Ahmed, who sees melanoma patients, at the time of her deposition she admitted, "I don't do anything special with them with respect to PDE5 inhibitors."

And so Mr. Imbroscio asked her the question, "So you

didn't ever tell anyone about it?" Very recently, quite recently, it had to be in the last year because it was since her deposition, there was a male patient that was taking PDE5 inhibitors and look what she told him outside the courtroom: "I told him there was research indicating there may be an association."

Think about the disconnect. She came into the courtroom and said, "Within a reasonable degree of medical certainty, there is causation." That is a totally different statement that she told a real-life patient. That is a huge *Daubert* red flag.

Dr. Singh, there was this colloquy with Mr. Brown. He says he's a public health scientist and it's his professional career that when he sees drug safety issues, he authors peer-review articles about them to raise awareness. That is what Dr. Singh's, according to him, his whole professional life is about. He didn't do it here.

He says that there's this big public safety issue -- and we'll talk a lot more about Dr. Singh in a second -- there's this big public safety issue he's identified with PDE5 inhibitors, which, by the way, are common medications -- right? -- tens of millions of patients. He says it's his professional career to publish peer-review articles when he spots those issues. He didn't do it here.

Why? Did we hear anything from Dr. Singh, Dr. Ahmed,

Mr. Cory, Mr. Meghjee why? Why haven't they tried to publish their articles or their opinions in peer-reviewed journals? I mean, I can speculate why. I think I know why. But whatever the answer is, they haven't even though in their normal day jobs this is what they do.

And Dr. Singh, actually he does it in litigation. I've been involved in a litigation with him, Mr. Brown has, where he does what he did here. He does an expert report claiming causation, and then he publishes it in the peer-reviewed literature. He didn't do that here. He's been retained for four years. That's a huge *Daubert* red flag.

Now, what do they do? They have failed the three *Daubert* factors pertinent to causation testimony and epidemiology. They don't have any general acceptance. They don't have any acceptance. They don't have peer review. They didn't submit their opinions to peer review.

And I should mention that, it's again undisputed, they didn't do any testing. Dr. Haq, you know, has his Haq Lab he said in Massachusetts where he does these types of tests. He didn't do it.

So they failed. There's no case that we found where someone fails the three *Daubert* factors and it's admitted, but it's theoretically possible. How do they get around it? They say, "We applied a method" -- I'm talking about the causation experts for a moment -- "Bradford Hill." Okay. Let's look at

it.

Everyone's in agreement that Bradford Hill is a two-step process. The first thing you do, and this is from Dr. Bradford Hill's article itself, the first thing you do is you have to find that there's an association that's a true association; in other words, it's not confounded. It can't be attributable to the play of chance. Everyone agrees that's step number one. You can't apply the factors unless you reliably satisfy that step.

And here we have a huge problem, and that is the confounding by sun exposure. Let me talk about the basal cell carcinoma data and the confounding because I think that's the crux of this issue.

Let me start with the study authors again. The study authors unanimously said that one of the reasons that they can't conclude causation or much of anything from their data, including I would point out the Li authors, that's who started all this, we cannot control reliably for sun exposure.

And if you think about that, you know why that is; right? You have to -- take the Li case, for example. They had to ask 60- and 70-year-old men "How many sunburns did you have when you were a child?" Now, I'm 53. Your Honor may be slightly older than I am. I don't know.

THE COURT: Just slightly.

MR. PETROSINELLI: You look great.

And so if someone asked me how many sunburns did I have when I was a child, I grew up near the beach, and then how many of those were blistering sunburns, it's impossible; right? It's an indirect way to imperfectly try to control.

But the Li study authors tell you that's not going to do it, and that is why -- remember, their conclusion was "Don't do anything with our data other than study it further. Don't alter clinical records. Don't stop prescribing Viagra to men, including men who have melanoma. Don't conclude cause and effect. We just need more study."

And all of these studies -- just let me say one thing that was not accurate, I believe, that we heard from the plaintiffs just now. Many of these studies, I won't say all of them, try to do the same thing. They tried to use proxies to control for sun exposure.

So, for example, I believe you heard the testimony some of them looked at socioeconomic status as a proxy. Of course, that's not a perfect proxy. It may not even be a great proxy but it's what you have.

And so you have this problem that the authors identified. What was the testimony from Dr. Singh and Dr. Ahmed about this? How did they reliably explain to you, or try to, that they reliably excluded it?

Dr. Singh said in his deposition Li's measure of exposure was the best but he said it was crude. And then Mr. Brown

asked him about that concession, and then he said, "Well, that's semantics. You know, I don't know what 'crude' means." He's the one who said it in his deposition.

How can a crude measure of sun exposure reliably exclude the possibility of confounding by sun exposure? It can't. It can't possibly be a reliable method to exclude.

Then what did Dr. Singh do? I think you remember what happened to Dr. Singh when he was on the stand. Let's do the chronology.

When confronted with the basal cell carcinoma data, in his report he offered no explanation of how it could be that basal cell carcinoma was also associated with PDE5 inhibitor use. In fact, I don't have it here on the slide. I just looked at it. In his report he said, "Well, maybe PDE5 inhibitors are protective of basal cell carcinoma, that they're good for it." That's what he said in his report.

They didn't like that. So when he got to his deposition, what he said in his deposition was, "Oh, it's looking at different kinds of sun exposure. Basal cell carcinoma is only caused by cumulative sun exposure; whereas, melanoma is caused by intermittent and so it's measuring different things and so it's not confounding."

What happened? The clinicians, the people who treat melanoma patients who the plaintiffs have, said, "That's not right. That is incorrect. Both basal cell carcinoma and

melanoma are both caused by all kinds of sun exposure."

And so at the hearing before you last week when he was confronted with, according to Dr. Haq, who I had cross-examined on this point and admitted it, "Yes, in fact, melanoma can be caused by either intermittent or cumulative."

So where did that leave him? He needed something else, and you may remember what he did. He said yesterday, 24 hours before he got on the stand, he found something new that explains the basal cell carcinoma findings. He found in one of the meta-analyses of a basal -- that found an association between PDE5 inhibitor use and basal cell carcinoma, he found that there was statistical heterogeneity yesterday. That was his third explanation, his third try.

And then I don't know if you remember what happened on recross. Mr. Brown showed him that the analysis he was relying on, this was the Feng meta-analysis, there was a typo. It was wrong. It had incorrectly inputted into the statistical data a wrong risk estimate. So not 15 minutes after he offered his third explanation, he had to recant it.

This is the antithesis of the scientific method. He was willing to come here on 24 hours' notice and tell you to a reasonable degree of medical certainty that the basal cell carcinoma confounding can be ruled out because of this; and five minutes later, he dropped it like a hot potato.

That is not the scientific method. That's what Dr. Singh

said about getting over this threshold hump you have to get over to get to even the Bradford Hill factors.

What did Dr. Ahmed say? Dr. Ahmed was pretty candid about this because, of course, she had to admit that, again, both types of sun exposure caused both types of these skin cancers; and she said, "Whether or not basal cell carcinoma is an appropriate measure of sun for melanoma, I'm not sure."

How can one reliably rule out the possibility of confounding if you're not sure? You can't. She can't reliably do it. They cannot explain why in study after study the risk estimates for basal cell carcinoma and melanoma in connection with PDE5 inhibitor use are identical.

Okay. One final point on this, Your Honor. I don't know if you caught this. This came out in Dr. Schuchter's testimony. There's actually a quite recent study, one of the most recent epidemiological studies, where they did something that's quite telling.

As I think you know, these medications are used for other medical conditions, most notably pulmonary arterial hypertension. In this study, the Shkolyar study, they looked at the association between use of these compounds for pulmonary arterial hypertension and melanoma or basal cell carcinoma.

And what did they find? No association whatsoever between use of the same compound, it's the same drug, and melanoma in this patient population. Pulmonary hypertension are these LUTS

patients.

And what does that tell you? There's something different about the erectile dysfunction population. For whatever reason, they have differentially high sun exposure, and that is why you see these very small but small, in some cases statistically significant, associations.

So they don't even get out of the *Daubert* box, their causation experts, on their method because they can't reliably rule out confounding. But let's say they did. Let's look at what did they do on Bradford Hill.

I put up again, Your Honor, these slides that come from the two recent MDLs, one in a device, one in a pharmaceutical product, where that these subjective factors and methods like Bradford Hill can be easily manipulated. And Dr. Singh, bless his heart, said the same thing, that "I agree, these are susceptible to sort of an outcomes-driven analysis." But he said, "I didn't do that here."

Let's look at what he did. First, as a general matter, you may remember this, not two years ago in the Lipitor MDL before Judge Gergel, who I actually have an MDL before right now, he's quite a science buff --

THE COURT: Judge Gergel in South Carolina?

MR. PETROSINELLI: Gergel in South Carolina.

THE COURT: A wonderful fellow.

MR. PETROSINELLI: And, you know, he was a plaintiffs'

medical malpractice lawyer and he loves the science and he digs in.

Before Judge Gergel, Dr. Singh came in and said, "Here are the Bradford Hill criteria. They're ordered most important to least." Two years later, here's his Viagra report. That sentence is missing.

And then you heard him on the stand say, "You know, over the last two years I've read a little bit more." By the way, he's been using Bradford Hill for about 20 years; but in the last two years, it just so happens that he's thought about it more and they're not ordered in importance.

Now, why would he do that? Might it be because when you look at the first four or five Bradford Hill factors here, several of them by his own admission are not present, like specificity and dose response? Huge *Daubert* red flag, changing your application of the method on the fly depending on which litigation you're in.

THE COURT: By the way, do you want to just comment while we're there on I asked Mr. Meghjee about how he assesses factor number one, strength of association?

MR. PETROSINELLI: Yes, I do.

THE COURT: Do you want to just tell me your view on that?

MR. PETROSINELLI: I will tell you -- I will do better than that, Your Honor. I will tell you Sir Bradford Hill's

view. The answer to your question is: It's the number. The strength of association means what is that relative risk number.

The thing about how many studies show it, that's a consistency factor. That's a different factor, which we'll talk about here. But the strength of association, Dr. Bradford Hill, when he described --

THE COURT: So, in other words, if you were looking at -- and I'm not as versed on the tobacco litigation that some of you were very well versed on, but my understanding I just gleaned from the discussion in our case here is that that may have been a circumstance in which the risk of association was relatively low. 1.2 or something was what some people suggested.

MR. PETROSINELLI: Yes.

THE COURT: But it's pretty clear now that there's a great -- there's quite a strong connection between tobacco and lung cancer. So is that one where if you're applying the Bradford Hill factor, you'd say that's a weak strength of association?

MR. PETROSINELLI: Correct.

THE COURT: Okay.

MR. PETROSINELLI: You'd say there's a weak association, but you'd say there's unbelievable consistency; right?

THE COURT: Okay.

MR. PETROSINELLI: And you would say it's a known carcinogen. Remember, those are secondhand smoke studies --

THE COURT: Correct.

MR. PETROSINELLI: -- not primary smokers. You would say tobacco is a known carcinogen, it's a known mutagen. Here everyone agrees PDE5 inhibitors are not carcinogenic and they've ruled out confounding and so on. So that's a totally different situation.

THE COURT: Okay.

MR. PETROSINELLI: Bradford Hill actually uses smoking when describing the strength of association. He said when he's describing strength of association (reading):

> "I've noted that the death rate from cancer of the lung in cigarette smokers is 9 to 10 times" -- so the relative risk is 9 or 10 -- "in nonsmokers and the rate in heavy cigarette smokers is 20 to 30 times."
>
> Then he says (reading):
>
> "On the other hand, you see some things where the association is no more than 2, possibly less. Those are likely confounded."

That's what strength of association is. It's totally contrary to the way that Dr. Singh described it on the stand.

Now, what did he say about this? First, we confronted him with one of the plaintiffs' own studies, which actually makes

my point again that this is what strength of association is about, the number. This was a plaintiffs' exhibit that was used, and here's the chart describing how, at least in this author's -- or these authors' views, what you would call an association that's between 1.0 and 1.2, by the way, where all the meta-analyses in this case are. None. Not even weak. None. Why none? Because it's so small and you can't rule out confounding and there's always confounding in epidemiological studies.

And 1.2 to 1.5, weak. We asked Dr. Singh about that, both in his deposition and at the hearing. Let's follow his method.

In his deposition we said, "Do you agree with" -- we actually showed him another study where a risk ratio below 2 was characterized as weak. "Do you agree that's weak?" "Yes."

Then what did he say in the hearing when we asked this? (reading)

> "I'm not in favor of nomenclature about weak and strong."

The factor is called strength of association. He just testified below 2.0 was weak, and then he said at the hearing before you, "I'm not in favor of talking about weak and strong."

And then we asked him, "Well, so what's the association? How did you weigh this?"

Here's what he said: "I weighed it strongly."

So he's assessing strength of association. He agreed in his deposition anything under 2 was weak. He said at the hearing he doesn't like to talk about weak and strong. And then when he was asked how he weighed it, he said, "I weighed it strongly."

That's a mess, Your Honor. It's not reliable science. It is not a reliable application of this particular Bradford Hill criteria.

I should also say to the Court because this relates to Roundup, in Roundup several of the studies were over 2.0. Some of the studies weren't; right? There was a fight in Roundup about which is the better study. We don't have that here. We don't have any 2.0s and over. In Roundup, there was evidence of dose response in some of these studies. We don't have that here. I'll touch on that in a second.

But this is how Dr. Singh came around to telling you that he weighted the strength of association factor heavily in favor of causation. Totally unreliable.

What did Dr. Ahmed say about this? She said -- you might remember because you actually had a -- I was noticing last night you had a little colloquy with her. You had asked her a question about it. She said (reading):

"I can't put a number on it. I can't give you even one number. I can't give you a range of numbers. What I

did is I looked at the totality of the studies."

Now, as we just discussed, she's now talking about the wrong factor. That's consistency. But even if you want to say that's strength of association, if you're judging an association strength, what is it; right? It has to be something.

And if you say -- if your answer to that is, "I'm looking at the totality of the evidence," that's a way to mask unreliable methodology; right? That is exactly what the courts say that assess these Bradford Hill analyses is unreliable by just saying, "You know, I looked at the totality and I used my judgment." Not good enough. That's what Dr. Ahmed said.

Dose response. The Li study. One thing that's been perhaps lost a little bit here, the Li study said, "By the way, if everyone's going to look at this now, please look for dose response evidence." Right? They said because, if you remember right, they were the one study, and everyone agreed this was a limitation, they couldn't measure the dose because they didn't have prescription records. And they said, "If we had dose in frequency and we saw something in a dose-dependent manner, that would be really important."

What happened? We have the concession from both Dr. Singh and Dr. Ahmed there is no -- in any of this epidemiological data, there is no dose response evidence, again, contrary to many of the cases that you see where there is such evidence.

And this chart, just so you see what it is, Dr. Witte had actually plotted all of the dose response evidence from all the epidemiological studies; and the idea is, I'll just do one of them, if you look at Matthews, one prescription it was 1.0; two to four, it goes up a little; then five to nine, it goes down; then 10 to 19, it goes up; and then greater than 20, it goes down. Right? Completely contrary to a dose-response effect.

So undisputed, that factor, I think by their own admission, does not support their causality opinion. And in most cases in a pharmaceutical context dose matters; right? It's a huge factor.

Let's talk about consistency because this is the other big thing. I showed this slide in opening. These are the 12 studies and meta-analyses. Now, only in some alternate universe could someone say that the Li study, and it's both its relative risk and its confidence intervals, is consistent with the rest of the data.

The only consistency you see here is everything below Li, these small associations -- some of which, by the way, are not statistically significant -- it's all hovering around 1. That's what the data shows.

What did Dr. Singh say? Dr. Singh showed a slide. It's a very interesting slide. This was his consistency slide. You might notice that this chart looks a lot different than the one that I used. Why does it look a lot different? Dr. Singh did

two things. First, he included this (indicating). This is the Ma abstract. It's not a peer-reviewed article that lays out its findings. It has never been published, but he put it there because, of course, that makes Li look a little more consistent; right? It's a little -- it's to the right even of Li.

But then when confronted about it, he said, "I didn't place a significant amount of weight on the abstracts. I couldn't evaluate them."

Why did he put it in the chart? How does it support his consistency conclusion if he can't -- as he said, "I couldn't really be subject to my quality assessment"?

And then he did this little sort of sleight of hand, this is not to scale. If you look at the bottom, .5 to 1 is the same distance as 1 to 2, is the same distance as 2 to 5.

So when you plot it like this, they look a little tighter, they look a little bit more consistent. That's not reliable methodology to support consistency.

And you might remember Dr. Singh saying when he first prepared his expert opinion, he wrote in his report five of the six studies that were then in existence were statistically significant. And he made a mistake, it was three of the six but, yet, he concluded that there was consistency.

To save time, Dr. Ahmed did the same thing. She put up a chart not drawn to scale with the abstracts.

Okay. Biological plausibility. So my first mention of this. It's my first mention of this because, as I said in my opening, all the very fascinating things we heard about cancer biology are relevant only insofar as that's one of the nine Bradford Hill criteria.

Of course, again, if Dr. Singh and Dr. Ahmed are excluded, this sort of doesn't matter, but I'm going to quickly talk about it because Your Honor asked a couple of questions of plaintiffs' counsel about this.

This was a board that I thought was quite useful that Mr. Holian used with Dr. Marais. So remember what they're saying here. It's not carcinogenic. It causes growth or invasion. Those are two different things.

Let's look at the right. On invasion, they had these three studies that they relied on. The Dhayade study and Zhang study they agree say nothing about invasion. The Arozarena study has no confirmation in the mice. Remember, the mouse testing didn't show invasion. One cell line *in vitro* showed invasion. They're saying it's biologically plausible based on test in one cell line *in vitro* in Arozarena.

On growth, Arozarena and Zhang say nothing about growth. Dhayade they had the mouse test. And Your Honor is exactly right, the question was the dose.

Okay. So this slide, I'm not going to go through this but I wanted the Court to have it. We'll obviously give you a copy

of the slides.

If you want to know what our criticisms were of the reliability of relying on these studies for biological plausibility, there are these. You see one that Your Honor raised, the B16 mouse.

But the other thing is, you might remember, every cell that was tested in the *in vitro* experiments in these two studies was metastatic already. It was taken from a human donor if it was a human cell. It had already invaded and grown. And the B16 mice, you're absolutely right, they don't have the mutations of human melanoma.

And so Dr. Haq, I think pretty candidly, said inconsistent results of growth, Arozarena's -- I mean, Dhayade is not as robust. And then he said this thing which, as you might remember in Dhayade, the other criticism was every time they tested Viagra, they used another chemical, he said, "Well, that was not to mimic human biology."

That's a fit point; right? The other *Daubert* factor is it has to fit. You have to extrapolate and there can't be an analytical gap, and this is what the evidence showed.

But on dose, this is the only evidence. The human dose -- a maximum human dose of Viagra is that, one pill. In the Arozarena study they gave the mice seven pills, 1.3 milligrams per kilogram seven days. And that was the dose in Dhayade.

Now, does that mean it's a crappy study? No. It's a

study that is trying to look at certain things, but you can't take from this with this dosing and extrapolate the humans reliably.

Another difference with Roundup. You might remember in Roundup Judge Chhabria said, IARC, the International Agency for Research on Cancer, they had evaluated the animal studies that were done on glyphosate and found that the doses that were given were replicated in terms of what humans might experience. And there's a line in Roundup that said if you have studies that have massive doses that are given to animals, you cannot reliably extrapolate from humans.

The final point I guess I want to make about biological plausibility is, Mr. Meghjee did this, yes, it is true, unlike the causation opinions, there are some epidemiologists who have made statements like this, may be biologically plausible, potential, and so on; but, of course, we're missing the larger point. In every one of these studies, what did they conclude about causation when they looked at their data? Can't conclude causation.

So biological plausibility, you know, it's one of the nine factors. I don't think what they've done is reliable but surely when it's weighed against the human data and all the other factors we've talked about in Bradford Hill, Dr. Singh and Dr. Ahmed did not do what the case law says you have to do with an inherently subjective test like this, which is reliably

explain why they discounted -- or how they even defined strength of association, dose response, consistency, specificity.

I thought this kind of to me encapsulated a quick point about their unreliable methods. Coherence is a factor, and Dr. Ahmed I thought said -- here's her slide -- well, it's coherent because the biological studies are consistent with the epidemiologic findings. And that's what coherence is; right? You see some in animals.

But then she was cross-examined about a point that Dr. Schuchter later made, which is this (reading):

> "On the laboratory studies we saw it showed growth, it showed invasion; but when you look at the epidemiologic data, your endpoint is very different. It's do you have melanoma or not. It's initiation, yes or no."

So she said the biology studies and the epidemiology studies are looking at two very different things, but yet she says there's coherence. Just another quick example.

So at the end of the day, what do we have? I suggest to you one way to look at this evidence in totality is that when you look at the scientific community, what are the things that they over and over again focus on in finding no evidence of causation? The confounding, the small or weak associations, and the no dose response. Every single one of the constituencies mentioned on this slide focuses on those three

things and finds insufficient evidence of causation.

So I finish really where I started, Your Honor, which is that we have a case here, we're lucky in the sense that it did take some time to get to this phase from the time the first study was published. Science worked.

Dr. Li and his colleagues came out with this study in which they themselves identified four weaknesses. We had a small sample size, which of course affects those wide confidence intervals. We had no information on dose. We can't rule out confounding. We can't prove cause and effect. They said, "No one change anything, but please study this."

And that's what happened. Over these last five years while we've been here litigating, science has moved forward and you've had all of this data, all the things that I showed you.

And what did the -- it's not just that the data and the researchers found no causation. It's that they looked at all these four things that started -- in a study that started this litigation. They looked at now four-plus -- if you combine all the epidemiology studies, we now have four-plus million people who have been studied. And, of course, with that wider number of people, that's why the risk estimate has become so weak. It has shown what the risk estimate is unadjusted for confounding, but the risk estimate.

Dose. They have information on dose. They have prescription records, and what they found is, everyone agrees,

what Li said you should look for if this is truly causal, no dose-response relationship.

Confounding. They've looked at confounding. They looked at the basal cell carcinoma. They ran the basal cell carcinoma tests and they found confounding, and none conclude causation.

And so at the end of the day, you have this (indicating). You have the entirety of the scientific community, everyone you could conceivably think of -- regulators, medical researchers, medical organizations, authors who've done Bradford Hill analyses -- saying that this scientific evidence does not reliably show causation.

And then you have Dr. Singh, Dr. Ahmed, and Dr. Liu-Smith, who we haven't talked about but the plaintiffs have said sort of her opinion is parallel and sort of rises and falls with the other two, are the only people, as far as we can tell, in the world, that is not an exaggeration, who have looked at this data and concluded causation. It is a huge, huge *Daubert* red flag.

I should say Mr. Meghjee ended where he showed this article from 2018 that he handed up, which says, he said, it shows it's still sort of an open question. I was surprised to hear that because when I read the one sentence in the article that relates to PDE5 inhibitors, which is on the second page of the article, it says in the right column, second paragraph down (reading):

"PDE5 inhibitor use has been associated with an increased risk of developing melanoma. A meta-analyses of five observational studies found a slightly" -- meaning weak -- "increased risk, 1.12. However, there were no prospective studies available for analysis to confirm the association."

The medical community has spoken. As I said to you in opening, Your Honor, with drugs like these that are prescribed still today every day, since we've been in this courtroom, a dozen men with melanoma have been prescribed these drugs. People would be shouting from the mountaintops if there was any chance that these drugs accelerated the progression of a deadly skin cancer because, of course, the population of people taking these drugs are generally older, higher risk for melanoma. Not only are they not doing that, people have figured out what that original Li study with its acknowledged weaknesses was about.

And so I would say to the Court that they have not satisfied a single one of the *Daubert* factors: General acceptance, peer review, testing. That, to my mind, is almost immediately disqualifying and it's undisputed.

And the way they've tried to get around it is the application of a method that while reliable in the abstract, you heard Dr. Singh, Dr. Ahmed, they did not reliably apply it to this case as shown by what everyone else has said, and we'd ask for their exclusion.

THE COURT: Thank you.

Any concluding comments? Anybody? Mr. Imbroscio?

MR. IMBROSCIO: No, Your Honor. Thank you.

THE COURT: Okay. Mr. Meghjee, no?

MR. MEGHJEE: No, Your Honor. Thank you and the court staff.

THE COURT: Well, thank you.

Very interesting case, very interesting presentation the last few days and today as well. So I thank you. I know how much work on both sides went into trying to educate me on this, and I very much appreciate it and it was superbly presented.

So now I have my work to do. I will go back and do the best I can, and we'll go from there. So thank you very much.

ALL: Thank you, Your Honor.

(Proceedings adjourned at 11:27 a.m.)

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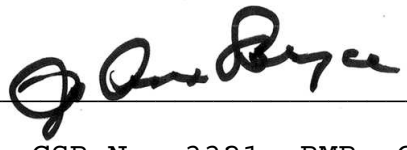
CERTIFICATE OF REPORTERS

I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter.

DATE: Tuesday, October 22, 2019



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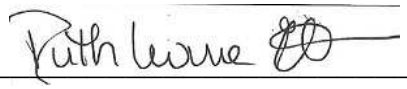

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